REMARKS

Entry of this Amendment is proper under 37 C.F.R. 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not introduce any new claims; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

As stated in the Office Action Summary, claims 1-8 are pending. Claims 1-4 and 7-8 are amended herein. Basis for the amendments may be found throughout the specification and claims as-filed, especially at claims 2 and 3 as-filed.

Claims 5-6 are canceled without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present amendment.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-2 and 7-8 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Office states that the relevant art is highly unpredictable with regard to therapeutic effects, side effects, and toxicity generated by drug-drug interactions when administering the combination of a β2 adrenoceptor agonist, which may encompass more than a thousand compounds, and loteprednol,. Without acquiescing in the rejection, and in the interest of expediting prosecution, independent claims 1, 7, and 8 are amended herein to recite specific β2-

adrenoreceptor agonists which are discussed in the working examples of the present specification. The combinations currently claimed are specifically disclosed in the present application, and so issues such as side effects and toxicity are moot. As the claimed combinations are disclosed and discussed in the examples of the present application, Applicants submit that no undue experimentation would be required to make and/or practice the presently claimed invention, and respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite, for the recitation of "pharmaceutically effective ester". The Office states that the skilled artisan would not know which the two moieties for the loteprednol ester are intended.

Without acquiescing in the rejection, and in the interest of expediting prosecution, claim 1 is amended herein to recite the loteprednol etabonate moiety. Thus, this rejection is obviated.

Rejections Under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Doi, Koji (WO 9831343), Bjerkec, and van der Molen. The Office maintains that it would have been obvious to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a pharmaceutical composition method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration.

Applicants traverse. In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. 2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

The Office states that the cited references teach the administration of steroids with β2 agonists. Although the references do not disclose the combination of loteprednol etabonate with reproterol, salmeteraol, or formoterol, the Office argues that it would have been obvious to make this combination. Applicants disagree. First, Applicants note the significant reduction in side effects seen with loteprednol, when compared to the use classical corticosteroids (please *see* Table 3). These data show that loteprednol, as a soft steroid, can not be equated with other, classical steroids, as there are different mechanistic properties between these two groups of steroids. Thus, although steroids are useful for the treatment of asthma and airway disorders, there is no motivation for the skilled artisan to chose loteprednol rather than a classical corticosteroid, as loteprednol is different from the disclosed steroids.

Further, loteprednol exhibits less side effects, improved therapeutic breadth and an overadditive therapeutic effect in combination with the disclosed β2-adrenoreceptor agonists. However, none of the references disclose any of these advantages for loteprednol, whether used alone or in combination with a β2-adrenoreceptor. Thus, the skilled artisan would not be motivated to chose loteprednol over another steroid.

Applicants further respectfully submit that there is no motivation for the skilled artisan, because unexpected results are present with respect to the claimed invention. The presence of an unexpected, advantageous or superior result is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A. 1963).

The present specification provides support in the form of the experimental data provided in the examples. First, Applicants point out the data shown with regard to the inhibition of TNF α release by the combination of loteprednol and salbutamol (*see* Table 1) which is overadditive in comparison to the administration of both substances alone. Table 2 illustrates the effect of the combination loteprednol and formoterol on the inhibition of eosinophilia which is also significantly overadditive compared to the single substances.

In light of the above comments, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

VA 692090.1